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Persistent inflammation with pedal osteolysis 1 Year after Charcot neuropathic osteoarthropathy

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Structured Abstract

Aims—To determine local and systemic markers of inflammation and bone mineral density (BMD) in the foot and central sites in participants with diabetes mellitus and peripheral neuropathy (DMPN) with and without acute Charcot neuropathic osteoarthropathy (CN).

Methods—Eighteen participants with DMPN and CN and 19 participants without CN had foot temperature assessments, serum markers of inflammation [C-reactive protein, (CRP) and erythrocyte sedimentation rate, (ESR)] and BMD of the foot, hip and lumbar spine at baseline and 1 year follow-up.

Results—CN foot temperature difference was higher compared to DMPN controls at baseline (4.2 ± 1.9 °F vs. 1.2 ± 0.9 °F, $P < 0.01$) and after 1 year (2.9 ± 3.2 °F vs. 0.9 ± 1.1 °F, $P < 0.01$). Serum inflammatory markers in the CN group were greater at baseline and remained elevated 1 year later compared to DMPN controls (CRP, $P = 0.02$, ESR, $P = 0.03$). All pedal bones' BMD decreased an average of 3% in the CN foot with no changes in hip or lumbar spine. DMPN controls' foot, hip and lumbar spine BMD remained unchanged.

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Disclosures

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Conclusions—Local and systemic inflammation persists 1 year after CN with an accompanying pedal osteolysis that may contribute to mid foot deformity which is the hallmark of the chronic Charcot foot.

Keywords

Charcot foot; inflammatory osteolysis; bone mineral density

1. Introduction

Acute Charcot neuropathic osteoarthropathy (CN) is a non-infective bone and joint destruction characterized by the onset of a red, hot, swollen foot in the presence of a dulled sensation to pain impairing function, mobility and walking. Acute CN inflammation can lead to an accelerated pedal osteolysis [30] contributing to rife sequelae, most notably acquired mid foot deformity [14] that is the hallmark of the chronic Charcot foot. [24] Persistent local or systemic inflammation with osteolysis can contribute to any number of poor outcomes including plantar ulceration, infection, and ultimately lower extremity amputation. [10, 20, 33]

Acute CN has long been associated with increases in local skin temperatures. [2, 3, 15, 30] Typically, skin temperature differences between feet of non-diabetic, non-neuropathic individuals vary little (e.g., 1.8 °F or 1°C). [30] However, in individuals with diabetes mellitus and peripheral neuropathy (DMPN), temperature difference between active Charcot and non-active foot have been reported to range from 9.2 to 26.5 °F (5.1 to 14.7 °C). [2, 3] The utility of monitoring temperature difference between Charcot and non-Charcot feet for clinical decision making is not without controversy. McCrory and colleagues questioned the utility of temperature differences to reflect the healing of acute Charcot fractures treated by total contact cast immobilization. They concluded that temperature difference may indicate a resolving inflammation, though an unreliable measure for clinical decision-making. [18] More recently, Ruotolo and colleagues showed that normalization (i.e., reduction) in skin temperature difference does not reflect the persistent bony inflammation as demonstrated by enhanced uptake of ¹⁸F-FDG uptake on PET/CT scans. They concluded that skin temperature monitoring to quiescence is an insufficient and misleading clinical criteria to establish when the acute inflammatory process is completely over in pedal bones, therefore normalization of skin temperature difference is not a sensitive parameter to drive therapeutic decisions. [25]

Despite the recognized need for resolution of acute inflammation in CN, there also remains some controversy whether there is an accompanying systemic inflammatory response in neuropathic individuals with acute CN. [22] Petrova and colleagues reported an average increase of 5.6 °F (3.1°C) in Charcot foot temperature in 36 consecutive patients on presentation to a diabetic foot specialty clinic. Despite the local inflammation, they observed only a small elevation in serum markers of inflammation. They found a median concentration of C-reactive protein (CRP) of 5.8 mg/l with 47% of the patients having CRP levels in the normal range (e.g., 5 mg/l). Additionally they reported a median serum erythrocyte sedimentation rate (ESR) concentration of 21 mm/hr which was mildly elevated.

[22] These findings require confirmation including follow-up over time after resolving acute inflammation.

There have been few clinical reports directly linking inflammation to pedal osteolysis in individuals with DMPN and acute CN. In a case-control cohort study, Sinacore and colleagues reported the Charcot foot had an average 3.7 °C (6.7 °F) higher skin temperature with an 18% lower calcaneal BMD than the non-Charcot foot. [30] Petrova and Edmonds found an 8% lower calcaneal BMD in the Charcot foot compared to the non-Charcot foot at presentation prior to cast immobilization attributing the pedal osteolysis at presentation to a higher skin temperature difference of 3.5 °C (6.3 °F) in the Charcot foot. [23] In a 2013 study, Gutekunst and colleagues reported that individuals with DMPN and acute CN had a 14% and 11% lower BMD in the 2nd and 5th metatarsal, respectively, compared to an age-matched group of individuals with DMPN but without CN. [12] These few reports support the hypothesis that inflammation may have an incipient causal role in acute CN with accompanying bone loss. [17]

Several studies have reported the natural history and long-term follow-up of feet after acute CN [2,10] however, there have been no previous reports of local and systemic inflammation with pedal and central site assessments of BMD 1 year after CN. Spontaneous new and recurrent neuropathic fractures are well-documented outcomes following CN as are acquired mid foot and hind foot deformities. [11,13,14] However it is not known if osteolysis accompanies a persistent inflammation or if BMD recovers within 1 year after CN. It is possible that often reported poor clinical outcomes, complications and sequela may be related directly or indirectly to the resolution of inflammation and the recovery of pedal BMD including adequate fracture healing and bony consolidation. Similarly, it is also unclear whether local changes in pedal BMD are reflected in central BMD sites (e.g., hip and spine) that are more routinely assessed. Therefore, the purposes of this study were to: 1] determine both local and systemic markers of inflammation and BMD in feet and central sites in participants with DMPN with and without acute CN at baseline and at 1 year follow-up assessment; 2] examine the relationship between local and systemic markers of inflammation with pedal BMD at baseline and 1 year follow up. We hypothesized local and systemic markers of inflammation would be reduced 1 year after CN onset and be similar to DMPN participants without CN and there would be no association between inflammation markers and pedal BMD. In addition, we hypothesized that foot and central site measures of BMD in CN participants would not be different 1 year after acute CN compared to baseline values due to resumption of daily weight bearing activities such as walking and standing.

2. Materials and Methods

2.1. Participants

We recruited participants with DMPN with and without acute CN. Participants with DMPN without CN were recruited at Washington University School of Medicine and surrounding areas from: 1] our medical center's volunteer research participation registry, 2] recruitment notices posted throughout our medical center, 3] contacts with community orthopaedic surgeons and podiatrists, or 4] from our Wound and Ostomy specialty clinic. Participants with CN were either referred from our diabetic foot specialty clinic to our physical therapy

service for total contact cast (TCC) immobilization over a 36-month period or recommended for participation by community orthopaedic surgeons or podiatrists. Inclusion criteria for all participants were previously diagnosed with diabetes mellitus (type 1 or type 2) and PN by a physician or were taking medications or exogenous insulin to control their blood glucose levels. [1] Participants with DMPN and CN had a physician-diagnosed CN (Eichenholtz stage 1, 2 or 3) based on a radiograph-confirmed overt fracture, bony fragmentation or neuropathic joint change (subluxation or dislocation) consistent with CN and no evidence of local infection, osteomyelitis, or advancing cellulitis. Participants with DMPN and CN were eligible if they had a concurrent plantar ulcer since in our experience plantar ulcers typically heal prior to resolution of inflammation of acute CN. [31] Exclusion criteria for all DMPN participants were body weight greater than 350 lbs (DXA and CT scanner's weight limit), partial or complete foot amputation of tarsal and metatarsal bones and a history or active evidence of osteomyelitis. Participants with DMPN without CN were excluded for any history or current foot disease including pedal ulceration, fracture or fixed mid foot or hind foot deformities; history of foot or leg trauma, metabolic bone disease, kidney or liver disease or transplant, taking immunosuppressive medications, women on oral contraceptives, bone anti-resorptive agents or hormone replacement therapy.

Participant demographics were obtained by self-report at the time of the baseline visit. The average duration of time prior to seeking therapy for their CN was determined by participant interview and report. Each participant's body weight was measured on a calibrated balance scale and height measured using a scale-mounted stadiometer without shoes. All participants read and signed an informed consent outlining our research protocol. Our research protocol was approved by our Human Subjects Research Protection Office's institutional review board. Each participant was reimbursed a modest sum after each research data collection visit.

2.2. Peripheral Neuropathy(PN)

All participants were diagnosed with PN prior to enrollment in the study. PN was defined as inability to sense light touch (pressure) at any one of 7 locations on the foot (dorsal mid foot, plantar surface of the first, third, fifth metatarsal heads; medial and lateral mid foot and central hind foot) using a single-thickness (5.07/10-g) Semmes-Weinstein monofilament [4, 8, 30] or a vibration perception threshold (VPT) ≥ 25 V at the great toe with the Biothesiometer (BioMedical Instrument Co, Newbury OH). [4]

2.3. Foot Skin Temperatures

To confirm the presence of local foot inflammation, all participants had skin temperatures assessed with infrared dermal thermometry (Exergen Dermatemp DT1001-LN) at the same 7 standard locations on each foot including the CN location at baseline and 1 year. [30] Participants were asked to remove socks, hose and footwear and rest comfortably on an examination table for at least 15 minutes in a temperature controlled room. We performed 3 trials of skin surface temperature assessment at each location in a standardized, ordered sequence. [30] The 3 measurements taken at each location were averaged to obtain a single average skin temperature for each foot location. The average skin temperature difference at

each site in the foot without CN was subtracted from the CN foot and considered the measured skin temperature.

2.4. Systemic Serum Inflammation Markers

Each CN participant had serum chemistries determined at baseline visit, 6 months and 1 year baseline and 1 year in DMPN participants without CN. Systemic (serum) markers of inflammation included C-reactive protein (CRP) [21] and erythrocyte sedimentation rate (ESR). [34] The percent of glycosylated hemoglobin (HbA1c) was determined to confirm their DM diagnosis. [1]

2.5. Bone Mineral Density

2.5.1. Tarsal & Metatarsal—Each participant had a volumetric quantitative computed tomography (vQCT) scan of each foot to determine BMD of 5 metatarsal and 7 tarsal bones at baseline visit and 1 year. [6,7,32]. A Siemens Definition 64-Slice CT dual-source scanner (Siemens Medical Systems Inc., Malvern, PA) was used to acquire all foot images (only 1 radiation source was used for this study). The spiral CT images of each foot were acquired separately while the participant was supine on the scanner table with the foot resting on the table. The table was positioned at approximately 120 mm from the scanner's isocenter with the center of the foot (talus) placed at the center of the scan volume and the foot angled at 45° to the table surface (toes pointed away from the body). Scan volumes extended from the distal toes to proximally above the ankle joint so that all tarsals, metatarsals, and phalanges were included. The following CT acquisition parameters were used: 38.4-mm table increment per gantry rotation (64 slices $\times$ 0.6-mm collimation), 220 mAs, 120 kVp, pitch of 1, rotation time of 0.5 s, and a 512 $\times$ 512 matrix. With software available on the scanner, the CT data were reconstructed with a B70f kernel at 0.6-mm slice reconstruction intervals (no gaps). A solid QCT-Bone Mineral™ Phantom (Image Analysis Inc., Columbia, KY) was aligned parallel to the table and scanned in series with each foot scan during one continuous acquisition. The phantom had dimensions of 300mm $\times$ 152mm $\times$ 32 mm consisting of 3 rods (20 mm in diameter) with different concentrations of calcium hydroxyapatite embedded in a water equivalent polymer. For each CT scan, the phantom density data were used to calculate a calibration curve to convert the mean Hounsfield Units (HUs) to apparent BMD (mg/cm³ of calcium hydroxyapatite). Although we use the term 'BMD' throughout this study, our vQCT methods reflect "apparent" BMD since our BMD measure include not only mineral content (calcium hydroxyapatite) but also the marrow content. [19] When severe bony fragmentation precluded accurate BMD assessment, we report only the metatarsal and tarsal bones that appeared intact. If metatarsal and tarsal bones had been fractured and fragmented and may have been healing with bony consolidation, only the mineralized portion of these bones that exceed a threshold of 100 mg/cm³ are reported [6,32]. The precision and reproducibility of metatarsal and tarsal bone BMD and volumes with our vQCT methods have been previously reported. [7,32]

2.5.2. Total Hip & Lumbar Spine—In addition to the vQCT scans of the feet, each participant had a dual-energy x-ray absorptiometry (DXA) scan (Hologic Inc, QDR series Discovery, Bedford, MA software Version 12) of the hip and lumbar spine (L2–L4) at the baseline visit and after 1 year. Participants with body weight that exceeded the

recommended DXA table weight limit of 300 lbs (136 kg), the distal forearm was scanned with the participant seated and their forearm positioned beneath the scanner.

2.6. Foot Radiographs

Three views (antero-posterior, lateral, oblique) of weight-bearing foot radiographs were obtained on each participant at or around the time of the baseline visit. Staging and primary anatomical location of each CN were determined by a single research team member (JEJ) who is a board-certified foot and ankle orthopaedic surgeon. All radiographs were de-identified and loaded into a Picture Archiving and Communications System, (ISite PACS, Phillips Healthcare Informatics, Foster City, CA) so the research team members were blinded to group status. Eichenholtz staging was used to stage each CN. [9] Eichenholtz staging is a temporal system based on radiographic appearance of the foot. Stage I is the fragmentation or dislocation phase in which clinical signs of inflammation are present and fractures, joint subluxations, dislocations, and deformities are visible on radiographs. Stage II is the coalescence phase with bony resorption or fusion of bony fragments. Stage III is the consolidation phase, during which fractures are healing and the foot becomes stable. Shibata et al. later added Stage 0, a stage in which the foot shows clinical signs of inflammation with limited or no radiographic evidence of bony fracture or joint subluxation. [28] The anatomical location pattern scheme proposed by Schon et al. was used to estimate the primary location of CN. [26] Schon et al. identified four patterns of locations: type I (Lisfranc pattern), type II (naviculo-cuneiform pattern), type III (peri-navicular pattern), and type IV (transverse tarsal pattern). If the pattern involved more than one location, the reviewing research team member identified the pattern as mixed.

2.7. Immobilization, Offloading and Prescriptive Footwear after Healing

The method for immobilization, the offloading device, as well as the duration of offloading and immobilization varied according to each participant's referring physician or health care provider and therefore was not standardized as part of this study. Prescriptive footwear was recommended for each participant with CN after healing. [31]

2.8. Statistical analysis

Group's physical characteristics were compared using two-sample, independent t-tests or Kruskal-Wallis non-parametric tests for sex, race, diabetes type and frequency of neuropathy. Foot skin temperature difference, serum markers, vQCT-derived BMD of pedal bones and DXA-derived total hip, lumbar spine and distal forearm BMD were compared using a Group by Time repeated measures analysis of variance (ANOVA). All BMD analyses were adjusted for differences in body weight between groups at baseline. Foot temperature differences and serum marker levels were compared at baseline, 6 month and 1 year using one-way, repeated measures ANOVA in CN participants. CN pedal bone changes over 1 year were analyzed as discrete bones and as averages of 7 tarsal and 5 metatarsal bones using one-tailed paired sample t-tests. Bi-variate associations between local and systemic markers of inflammation and pedal BMD were determined using Pearson correlation coefficients with baseline and 1 year values from both groups. An alpha level of 0.05 was used to indicate statistical significance. All statistical analyses were performed in IBM SPSS Version 20 software (IBM Corp, Armonk, New York).

3. Results

Demographic and physical characteristics of each group are shown in Table 1. We recruited 40 participants, with 20 participants per group, however 2 CN participants and 1 DMPN participant did not provide 1 year follow up data so were excluded from the analysis. Both groups were matched in physical characteristics except for body mass which was greater in CN participants. All participants had PN confirmed at their baseline visit. The interval of time from onset of symptoms to the initial baseline skin temperature assessment and start of immobilization in the participants with CN was estimated from the participants' interview to be 4 to 7 weeks. Twelve of 20 (60%) participants reported that their current CN was their first onset, whereas 8 participants (40%) reported at least one prior onset in the same foot location or in a different location within the same foot. No participant with CN had been diagnosed with renal or hepatic osteodystrophy, none stated they were current smokers, and one reported taking oral steroids for asthma within the past 2 years. All female participants reported they had undergone menopause and were not receiving hormone replacement therapy or oral contraceptive therapy. Four of the 20 participants (20%) recruited with CN had an accompanying non-infective plantar ulceration. The plantar ulcer was remote from the primary fracture or joint dysfunction in 2 participants and was directly beneath the fracture or subluxation location in 2 participants. All CN participants were classified as Eichenholtz Stage 1 with primary anatomical location in CN feet shown in Table 1.

3.1. Foot Skin Temperature

Figure 1A & B show the foot temperature difference at baseline and 1 year later. The CN group's foot temperature difference at baseline was 4.2 ± 3.6 °F (2.3 ± 2.0 °C) compared to the right-left foot difference of 1.2 ± 1.5 °F (0.7 ± 0.8 °C) in the DMPN controls, ($P < 0.01$). After 1 year, CN foot temperature difference was 2.9 ± 4.0 °F (1.6 ± 2.2 °C) compared to right-left foot difference of 0.9 ± 0.9 °F (0.5 ± 0.5 °C) in the DMPN controls, ($P < 0.01$).

3.2. Systemic Serum Inflammation Markers

Figure 2A & B show the systemic markers of inflammation at baseline, 6 months and 1 year follow-up. Serum CRP and ESR were elevated at baseline, decreased at 6 months and increased back to baseline values 1 year after CN. In CN participants at the 6 month visit, CRP ($P = 0.01$) and ESR ($P = 0.04$) decreased after immobilization with offloading. In DMPN controls, CRP and ESR were lower at baseline ($P = 0.02$) and remained lower 1 year later ($P = 0.03$) compared to CN participants.

3.3. Bone Mineral Density

Bone mineral densities of the metatarsal, tarsal, total hip, lumbar spine and distal forearm of CN and DMPN groups at baseline and 1 year follow-up are shown in Table 2. Though variable, metatarsals in the CN group all had lower BMD at 1 year follow-up. Metatarsal 1 and 5 *lost* an average 7.6–8.2% BMD ($P = 0.04$), while metatarsals 2, 3 and 4 *lost* 1.5–7.2 % ($P > 0.05$). Some tarsal bones (e.g. calcaneus, talus, navicular, 1st cuneiform) *lost* 2.7–6.9% BMD after 1 year ($P > 0.05$) while other tarsal bones (e.g. cuboid, 2nd & 3rd cuneiforms) showed 1.1–6.7% *increases* in BMD, ($P > 0.05$). We were unable to accurately measure the BMD of several tarsal bones (most often talus and navicular) in 3 participants in the CN

group due to severe destruction and bony fragmentation. DXA-derived BMD of the (total) hip, lumbar spine (L2–L4) and distal forearm were not different at baseline and did not appreciably change in CN or DMPN participants after 1 year. Figure 3A & B show scatterplots of all participants' average BMD of all pedal bones versus the foot skin temperature difference (A) and versus erythrocyte sedimentation rate (B) at baseline and after 1 year. Both local ($r = -0.29$, $P < 0.05$) and systemic ($r = -0.30$, $P < 0.05$) markers of inflammation are inversely related to the average BMD of all pedal bones.

3.4. Immobilization, Offloading and Prescriptive Footwear after Healing

Immobilization devices consisted of either total contact casting (TCC) with transition to a removable cast walker (RCW) boot for 10 participants or a RCW-boot for eight participants. Three participants had combinations of immobilization and offloading methods. Nine CN participants received treatment from one of the authors (DRS) while 9 participants received treatment from other providers (e.g., diabetic foot specialty clinics, community orthopaedic surgeons and podiatrists). CN participants were immobilized and offloaded with TCC or commercial RCW boots for an average of 19 ± 14 weeks. In the 4 participants with CN and an accompanying plantar ulcer, all received TCC immobilization with 3 of the 4 ulcers healing in 6 to 9 weeks. In each of these cases, either TCC or RCW immobilization was continued for several additional weeks after ulcer healing until their skin temperatures were reduced. One participant with mid foot ulcer did not heal and went on to have a trans-tibia level amputation 1 year after follow up. Most (72%) participants were returned to their prescriptive footwear after completing the immobilization and offloading therapy. Five participants (3 female) were prescribed either calf lacer with bilateral metal uprights (Gillette-type) bracing or Charcot restraint orthotic walker (CROW) boots to allow protected weight bearing after healing to resume protected walking.

4. Discussion

The major finding of our study is local and systemic inflammation persists 1 year after acute CN accompanied by an overall average decrease in BMD of all tarsals and metatarsals of 3%. We did not observe concomitant decreases in total hip, lumbar spine or distal forearm BMD in any of the participants. Local and systemic markers of inflammation with concomitant BMD in tarsals, metatarsals, total hip, lumbar spine or distal forearm 1 year after acute CN compared to a control group of DMPN participants without CN has not been previously reported. Systemic inflammation markers (CRP and ESR) were significantly higher in CN participants compared to DMPN controls at baseline and 1 year after CN. Both serum markers decreased significantly at 6 months, most likely in response to offloading and immobilization but returned to baseline values after 1 year presumably after resumption of full weight bearing activities and perhaps non-adherence to therapeutic footwear use.

Though the decrease in BMD for all participants and all pedal bones averaged 3%, we observed a highly variable osteolysis response and recovery among participants and discrete tarsal and metatarsal bones 1 year after onset of acute CN. Most CN participants showed small net losses (or small net gains) in pedal bones. Some CN participants gained in tarsal BMD and lost little in their metatarsals, while other participants showed considerable losses

in pedal bones 1 year after CN, including an average of 19 weeks of immobilization with offloading. Metatarsal bones in CN participants lost an average of 5.6% BMD, while several tarsal bones (e.g., cuboid, 2nd & 3rd cuneiforms) had small increases in BMD. Tarsal and metatarsal BMD in the CN foot were significantly lower (~12%) than the average of both feet in the DMPN control group at the baseline visit ($P < 0.05$) and ~15% lower at 1 year follow-up, ($P < 0.05$). These new findings add to our previous report using ultrasonometry, having observed the estimated BMD of the calcaneus in the CN foot was 18% lower than the contralateral, non-Charcot foot prior to offloading and 29% lower than feet of age- and gender-matched, non-diabetic, non-neuropathic individuals. [30] Interestingly, Petrova and Edmonds report a 5.2% lower QUS-estimated calcaneal BMD in the Charcot foot after 8 months of TCC immobilization to resolve the accompanying inflammation, [23] while we found a 5.5% calcaneal osteolysis after 1 year in the CN foot using our vQCT methods. Though the magnitude of pedal osteolysis due to CN is variable among participants and discrete bones, it can be quite profound and may (in part) be mediated by inflammation that persists following acute CN. [25] In support of the observation that persistent inflammation may be mediating pedal osteolysis is our finding that both foot temperature difference and ESR are significantly related to BMD in all participants, Figure 3A&B. Therefore, continuous monitoring of local or systemic markers of inflammation with pedal BMD may be required to determine the complete impact on CN outcomes.

Hyperglycemia and systemic inflammation are the hallmarks of chronic DM and when combined with PN and an acute CN, may accelerate pedal osteolysis making the foot more susceptible to structural breakdown and acquired mid foot deformities [5,13,14]. Persistent (low-grade) local and systemic inflammation may in turn, attenuate or impede recovery of BMD after immobilization and offloading. [25] While no direct cause for pedal bone loss can be attributed solely to the persistent inflammation, it may be the incipient contributor to the progressive mid foot and hind foot deformities that have been reported after CN onset [13,14,25] that characterize the chronic Charcot foot [17,24]. We believe the clinical consequences of persistent inflammation and pedal osteolysis in CN may contribute to any number of the generally poor outcomes including plantar ulceration, infection, and ultimately lower extremity amputation that have been reported. [5,20,33]

We found no difference in DXA-obtained total hip or lumbar spine BMD in participants with CN compared to DMPN participants without CN at baseline or 1 year of follow-up. Herbst and colleagues reported that ipsilateral hip BMD predicted the pattern of CN (fracture versus dislocation) in a group of 55 consecutive patients presenting with CN. [16] They found significantly lower ipsilateral hip T-scores in patients with a fracture pattern compared to a dislocation pattern and a greater frequency of dislocation patterns with higher hip T-scores in mid foot and hind foot CN locations compared to the forefoot. [16] By contrast, we found total hip BMD was not different between groups at baseline, did not change appreciably 1 year after acute CN and did not correlate with either local or systemic indicators of inflammation (data not shown). Though we studied a smaller number of CN participants than Herbst et al, we could not discern that any single location or pattern of CN impacted hip BMD, therefore we conclude that BMD of all or select bones of the Charcot foot may be more informative of CN outcomes than the central sites of BMD at the ipsilateral hip or lumbar spine.

Limitations of our study include a small sample size and the lack of standardized offloading therapies to resolve acute inflammation. Only 3 participants had type 1 DM, therefore we were unable to detect or interpret meaningful differences in inflammation biomarkers or pedal BMD between the phenotypes of diabetes. Similarly, our study was not intended nor adequately powered to detect differences in participants with first-onset CN compared to repeated CN episodes, though bone loss may have been accelerated and recovery of pedal BMD may have been attenuated in participants with recurrent episodes of CN.

We could not detect a difference in use of a TCC or RCW offloading boot on inflammatory markers or pedal osteolysis in our participants, therefore the impact due to the type and compliance with immobilization device cannot be fully discerned from our study. Similarly, we cannot determine the extent of pedal osteolysis immediately after immobilization since we did not assess BMD at that critical time in this series of participants. Furthermore, due to the small number of participants with each pattern of acute CN, we cannot determine if anatomical location or pattern of CN had any discernible impact on the persistence of inflammation or pedal BMD. In a previous series of 40 patients with 51 CN feet, Sella and Barrette described that CN destruction typically starts along the medial column bones commonly involving the 1st and 2nd cuneiforms, articulating metatarsals and the talo-calcaneo-navicular joint. [28] These observations agree with our previous report of a 21% lower calcaneal BMD in individuals with medial-column type deformities compared to individuals who develop a lateral-column Charcot deformity phenotype. [29] Although we have observed progressive deformity along the medial column after CN [13,29], we could not distinguish any single pattern of CN resulting in greater inflammatory bone loss in our small series of participants. Anatomic location influences healing time of acute CN as does adherence with offloading and compliance with type of offloading device used, and the amount of weight bearing and walking activity during the acute stage. [31] Most likely several factors combine to impact the persistence of inflammation, pedal osteolysis and ultimately progression to foot deformity. [14,25] Finally, assessing vQCT-derived BMD of all pedal bones is somewhat labor-intensive since it requires segmentation of discrete tarsal and metatarsal bones and simultaneous image analysis with a known density phantom. We have found that vQCT-derived BMD of individual foot bones are reliable and precise assessments [6,7] that can inform the clinician of a complete recovery of BMD in all tarsal and metatarsals affected by acute CN. As pedal BMD methods are improved, refined and further automated for rapid interpretation, clinical decision-making after CN can likely be improved with the potential for better clinical outcomes. Further research on the impact of inflammatory osteolysis after acute CN should yield improved methods of therapy to improve outcomes including limiting pedal bone loss.

5. Conclusions

Foot and systemic markers of inflammation persist for 1 year after CN. Pedal osteolysis accompanies the persistent inflammation that may contribute to reportedly poor clinical outcomes including progression of mid foot deformities that characterize the chronic Charcot foot.

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Figure 1.

Local foot skin temperature difference ($^{\circ}\text{F}$) in CN and DMPN group at baseline visit and 1 year. Total foot skin temperature difference in CN group is affected foot minus unaffected foot from mean of all 7 sites (A). CN location skin temperature difference in CN group is affected foot minus unaffected foot (B). DMPN group is absolute skin temperature difference between right and left foot. Bar height represent mean, error bar is ± 1 SEM.

* $p < 0.05$ between groups at baseline and 1 year; $p > .05$ between baseline and 1 year in both groups.

Figure 2. Serum C-reactive protein (**A**) and erythrocyte sedimentation rate (**B**) in CN and DMPN groups at baseline visit, 6 months and 1 year. Bar height represents mean, error bar is ± 1 SEM. * $p < 0.05$ between groups at baseline and 1 year; $p > 0.05$ between baseline and 1 year in CN group and DMPN group. ** $p < 0.05$ CN group at baseline and 6 months.

Figure 3. Scatterplots of average pedal bone density of all bones versus foot skin temperature difference (A) and erythrocyte sedimentation rate (B). Data points are n=74 representing CN & DMPN groups at baseline and 1 year follow up.

Table 1

Physical and demographic characteristics of participants at baseline visit.

Characteristic	CN N= 18	DMPN N= 19	P Value
Age (years)	56 ± 10	57 ± 10	0.46
Race	5 AA 13 C	7 AA 12 C	0.55
Sex	9 Men 9 Women	8 Men 11 Women	0.63
HT (cm)	175 ± 8	172 ± 8	0.22
WT (kg)	113 ± 26	95 ± 26	0.03
BMI (kg/m ²)	37 ± 7	32 ± 8	0.06
DM Type	1 Type 1; 17 Type 2	2 Type 1; 17 Type 2	0.58
DM Duration (years)	17 ± 10	14 ± 13	0.10
Neuropathy (No. unable to sense 10-g monofilament)	18	16	0.20
Vibration Perception Threshold (V)	42 ± 7	35 ± 13	0.29
HbA1c (%)	7.6 ± 1.9	7.8 ± 1.4	0.39
No. Medications	11 ± 5	9 ± 3	0.11
* Anatomical Location (% of CN feet)	39% type I; 11% type I; 6% type III; 22% type IV; 22% mixed	NA	NA

Data are mean (± SD). NA=not applicable. AA=African American; C=Caucasian. No. medications include reported supplement use.

* Anatomical location based on patterns described in reference #26.

Table 2

Metatarsal, tarsal, hip and lumbar spine bone mineral density values at baseline and 1 year in CN and DMPN groups.

Bone	CN Foot Baseline	CN Foot 1 Year	% Diff	CN Foot Time P Value	DMPN Baseline	DMPN 1Year	% Diff	DMPN Time P Value	Group P Value
1 st Metatarsal	353	324	-8.2	0.04	443	444	0.2	0.96	< 0.00
2 nd Metatarsal	474	458	-3.4	0.44	571	573	0.4	0.94	< 0.00
3 rd Metatarsal	461	454	-1.6	0.48	538	543	0.9	0.86	< 0.00
4 th Metatarsal	458	425	-7.2	0.13	523	526	0.6	0.91	0.02
5 th Metatarsal	460	425	-7.6	0.02	535	534	-0.2	0.97	< 0.00
All Metatarsals	441	417	-5.6	0.07	522	524	0.4	0.93	< 0.00
Calcaneus	257	243	-5.5	0.03	314	311	-0.9	0.95	< 0.00
Talus	367	357	-2.7	0.16	403	400	-0.7	0.88	0.01
Navicular	407	379	-6.9	0.42	424	423	-0.2	0.95	0.08
Cuboid	298	318	6.7	0.02	291	291	0.0	0.99	0.47
1 st Cuneiform	361	348	-3.6	0.24	388	386	-0.5	0.91	0.03
2 nd Cuneiform	372	388	4.3	0.07	439	437	-0.5	0.90	< 0.00
3 rd Cuneiform	357	361	1.1	0.45	378	378	0.0	0.99	0.26
All Tarsals	346	342	-0.9	0.13	377	375	-0.4	0.95	0.01
All Bones	385	373	-3.1	0.37	437	437	0.0	0.99	< 0.00
Total Hip	928	930	0.2	0.87	1033	1034	0.0	0.99	0.12
Lumbar Spine	1119	1132	1.1	0.30	1103	1109	0.5	0.92	0.99
Distal Forearm	646	642	-0.6	0.26	596	591	-0.8	NA	NA

Data are group mean values. Metatarsal and tarsal BMD values are CN foot (non-CN foot values are not shown). DMPN values represent average of both feet. All pedal bone BMD values expressed in mg/cm³ except Total Hip and Lumbar Spine BMD values obtained with DXA are expressed in mg/cm². The % difference in 1-year values compared to baseline values with negative numbers representing group *loss* in BMD; positive numbers representing group *increase* in BMD. Time P values represent baseline versus 1-year comparisons in CN and DMPN feet; Group P values represent between groups comparisons combining both baseline and 1-year time points adjusted for group differences in body weight. CN Foot and DMPN Time P values represent one-tailed, paired sample t-tests comparing baseline and 1 year. Four participants in the CN group and 1 participant in the DMPN group had distal forearm measured due to DXA table weight restriction. NA is not applicable.